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09/464,795

APPLICATION NO. 09/464,795	FILING DATE 12/16/99	ZHANG FIRST NAMED INVENTOR	N	ATTORNEY DOCKET NO.
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ART UNIT

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/464,795	ZHANG ET AL.	
	Examiner	Art Unit	
	Ram Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 October 2000.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 38,41,43,45,46,49,and 65-68 is/are pending in the application.
- 4a) Of the above claim(s) 39,42,44,47,48,50, and 69-79 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 38,40,41,43,45,49,and 65-68 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☒ The proposed drawing correction filed on 16 December 1999 is: a) ☐ approved b) ☒ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- | | |
|--|--|
| 15) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 18) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 16) <input checked="" type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 19) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 17) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 20) <input type="checkbox"/> Other: _____ |

Art Unit: 1632

DETAILED ACTION

1. Amendment filed 10-25-00 has been entered.
2. Claims 1-37 and 51-64 have been canceled.
3. New claims 65-79 have been entered.

Election/Restrictions

4. Applicant's election with traverse of the invention of group I, claims 1-5 and 36-64 in Paper No. 5 is acknowledged. The traversal is on the ground(s) that invention of claims 51-64 are related to method of producing a transgenic non-human animal and that a related set of claims are being prosecuted in another application and have therefore been canceled. Applicants have added new claims 65-79. Applicants have further submitted that the invention of group I should be further restricted into two groups, one containing claim 38 and dependent claims and the other containing claim 39 and dependent claims. As submitted by the Applicants new groups VIII, IX, and X have been made as follows:

Groups VIII, claims 38, 40, 41, 43, 45, 46, 49, and 65-68, drawn to a transgenic non-human animal comprising a panel of expression cassettes.

Group IX, claims 39, 42, 44, 47, 48, 50, and 69-72, drawn to a cohort of transgenic non-human animals.

Group X, claims 73-79, drawn to a transgenic, non-human animal comprising an expression cassette wherein said expression cassette comprises control elements of an HO gene.

Finally, Applicants submitted that they would like to elect group VIII, claims 38, 40, 41, 43, 45, 46, and 49 for further prosecution.

Examiner appreciates Applicants' input in clarifying the restriction requirement. Newly presented claims 65-72 have been assigned to groups VIII and IX since they depend from claims 38 and 39 and the election of group VIII, claims 38, 41, 43, 45, 46, 49, and 65-68 is

Art Unit: 1632

made of record. These elected claims would be examined and the restriction is therefore made FINAL.

5. Claims 39, 42, 44, 47, 48, 50, and 69-79 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 5.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 38 and 65-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the revised interim guidelines on written description published December 21, 1999 in the Federal Register, Volume 64, Number 244, page 71427-71440(also available at www.uspto.gov).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Since it is not realistic to expect that the "complete structure" of any transgenic animal, or even a cell, could be described, this requirement is interpreted to be whether phenotypic consequences of altering the genotype have been described. In this case, the specification provides prophetic examples and methodology to make transgenic animals (see page 65, lines 2-7 and pages 65-68 of the specification). It is noted that the specification does not describe any working example of producing a transgenic animal and does not describe the characteristics of a transgenic animal encompassed by the claimed invention. It is further noted that considering the fact that the art of making transgenic animals is highly unpredictable, the phenotypes and characteristics of the transgenic animals encompassed by the invention are not

predictable. Additionally, due to the unpredictability of the site of integration of the transgene, one may not even know whether viable transgenic mice would have been produced, and therefore, it is not clear how can the transgenic animals encompassed by the claimed invention be described.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. It is not possible to adequately describe the claimed products because the effects of incorporating an exogenous gene by random integration can not be predicted. Cameron (Cameron ER. Molecular Biotechnology 7:253-265, 1997) noted,

" Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in nontargeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy- number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene" (see page 256, section 4 on transgene regulation and expression).

In the instant application, it is not clear what would have been the result of the incorporating one or more expression constructs in the genome of any and all transgenic animals encompassed by the invention or whether a viable transgenic animal with a certain phenotype would have been produced.

With the limited information disclosed in the specification, an artisan would have not been able to predict whether all these animals would have had same or different phenotypes. Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genera recited in the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera of the invention.

Art Unit: 1632

8. Claims 38, 40, 41, 43, 45, 46, 49, and 65-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Instantly claimed invention encompasses any and all transgenic animals (except human) that comprise a panel of expression cassettes wherein said panel comprises 2 or more expression cassettes which in turn comprise a control element from a stress inducible gene operably linked to a light generating polypeptide. Different expression cassettes in a particular transgenic animal may comprise control elements of different stress-inducible genes and different light generating polypeptides. Instantly claimed invention also encompasses methods of determining the effect of an analyte on gene expression mediated by selected control elements by administering the analyte to the transgenic animal and determining light generation from the light generating polypeptide in the transgenic animal under appropriate conditions.

The specification is not enabling for producing any and all transgenic animals comprising more than one expression construct because the specification does not provide sufficient guidance, evidence, and working examples to make all the transgenic animals and because the art of making transgenic animals is highly unpredictable. As the current state of the transgenic animal research stands, there are several significant limitations to the application of same methodology of making transgenic animals to different species. Longer gestation times, reduced litter sizes, number of fertilized eggs required for micro injection and relatively low

Art Unit: 1632

efficiency of gene integration and method of introduction of transgenes are a few examples of such limitations. Investigators observed 5-70 fold lower yields of a recombinant protein in transgenic mice when they used a construct designed for expression in sheep (see lines 1-12 in 4th para of col 1 on page 632 in Mullins et al. (Mullins JJ et al. Hypertension 22:630-633, 1993)). The variation in expression levels between different cell lines and species may be attributed to host genetic background, the site of chromosomal insertion and absence of specific transcription factors.

In a more recent assessment of the transgenic technology, Cameron (Cameron ER. Molecular Biotechnology 7:253-265, 1997) noted, " Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in nontargeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy- number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene" (see page 256, section 4 on transgene regulation and expression).

For example, Hammer et al (Hammer RE et al. Cell 63:1099-1112, 1990) created both transgenic mice and rats expressing human HLA-b27 gene and beta-2 microglobulin. Although, both the transgenic animals bearing HLA-27 gene expressed the gene, transgenic mice did not show any HLA-2 associated disease whereas the transgenic rats demonstrated most of the HLA-B27 related diseases (see lines 20-28 in col 2 of page 1099). This shows that the integration of a transgene into alternative species may result in widely different phenotypic responses even in animals of the same species. Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors. The specification does not provide any guidance as to whether a given promoter used for expressing an exogenous gene in one animal would have been functional in other animals and even if the promoter may have been active, whether the level of the transgenic product produced would have been sufficient to produce a certain phenotype. If not, what steps would have been taken to address this issue?

Art Unit: 1632

The production of transgenic farm animals and livestock species is further complicated. Seidel (Seidel GE. J. Anim. Sci. 71(Suppl. 3):26-33, 1993) noted "In the case of livestock species.....Characterizing a transgenic line often is a greater logistical undertaking than making the transgenic founder. Ideally, animals should be evaluated for the transgenic trait as well as for absence of undesirable side effects in both sexes in both the hemizygous and homozygous transgenic states. Producing homozygous transgenic animals requires mating relatives, resulting in inbreeding. Characterization of transgenic lines takes many years in species with long generation intervals."

Introduction of foreign DNA into fertilized oocyte, for example by micro injection, may result in random integration of the exogenous DNA into host chromosomal DNA which in turn may have major consequences on the expression of the transgene, therefore the production of transgene in all the non-human mammals species will be highly variable and unpredictable. While it is realized that making of a transgenic mouse has been more perfected over the years, as noted above by Cameron et al even making of transgenic mouse with a certain phenotype is not predictable because it is uncertain whether an artisan can produce a transgenic mouse of same phenotypes a second time using same expression construct. Regarding, transgenic animals of other species, it is highly unpredictable whether transgenic animals from all species will express a transgene to a level high enough so as to enable the method utilizing the claimed transgenic animals. Cui et al (Cui C et al. Transgenic Research 3:182-194, 1994) reviewing the state of the art of reporter genes in transgenic mice noted that when a lacZ construct was introduced in ES cells by electroporation and the resultant ES cells were injected in to blastocysts and whole embryos were tested for lacZ expression, each strain manifested a unique pattern of transgene expression indicating that the expression of the transgene is dependent on the site of integration (see last paragraph in column 1 on page 184). It is noted that in the instant case the transgenic animals comprise more than one expression construct, and when the expression of one construct is not predictable, it is not clear how can the expression of multiple expression vectors be predicted. Yet another unpredictability of making transgenic animals with reporter genes has been the unpredictability whether the reporter gene would be expressed post-natally, even if the reporter gene was expressed at the embryonic stage. Again Cui et al noted that that the same promoter that expressed reporter gene lacZ in embryo did not direct expression in adult (see column 2 on page 186). While Cui et al used the

Art Unit: 1632

example of lacZ, based on the prior art and the teachings of the specification, it is not clear whether the reporter genes of the claimed invention would have shown same level of expression in the embryos and adult animals.

Regarding the method claims (claims 40, 41, 43, 45, and 46), it is noted that if the making of the transgenic animals was unpredictable, it is not clear how would an artisan know how to use these transgenic animals in claimed methods without knowing the characteristics of the transgenic animals. In addition to the making of the transgenic animals encompassed by the claimed invention, the specification fails to provide sufficient guidance as to how an artisan would have used the claimed transgenic animals in the claimed methods. It is noted that the specification has cited US Patent 5,650,135 as the method of noninvasive detection of reporter gene expression. US patent 5650135, however, does not teach a method using a transgenic animal rather this method teaches monitoring luminescence in a transgenic mouse inoculated with bacteria containing an expression construct where dissemination of the bacteria in the body and expression of the luciferase gene may not be equated to a transgene integrated in the genome of an animal. Further, the claimed method of the instant application is different from the animal of the cited US patent because in the transgenic animals of the instant application, the transgenic may not be expressed to the same extent in all the cell types or tissues or sites in the body. Alternatively, different tissues of the transgenic animal may express the transgene to different levels. Additionally, in the claimed method first an analyte has to be administered to the transgenic animal which has to reach the control element of the transgene in the nucleus of a cell after it has entered a cell via a receptor or any other method and an analyte may affect more than one stress gene and the extent of effect may not be distinguishable from each other. The specification in pages 35-41 has disclosed an extensive list of gene whose expression is altered under stress and therefore, their control element may be used in the expression constructs in any combination of at least two control elements. However, the specification does not provide any guidance as to whether the activity of all these elements would have been affected by an analyte in vivo when the promoter is inserted in the genome not at its natural site. Additionally, the specification does not provide any guidance as to whether these control elements would have behaved in directing reporter gene expression as they regulate the expression of their natural coding sequences. After the luciferase enzyme is produced in a cell it has to interact with the substrate to emitting light, which would then be captured. Additionally,

the claimed invention recites more than one light producing polypeptides in a transgenic animal. A multitude of all these factors (one or more) will affect the final detection of bioluminescence and the specification does not provide any guidance as to whether the results obtained in the method would be a true representation of the changes in the promoter activity or the activity of the control element of several control elements present in the transgenic animal. Additionally, the method of the cited patent would target a bacterial cell comprising the transgene. In contrast, the instantly claimed method is intended to differentiate between the expression level of multiple promoters or control elements in the absence or presence of an analyte that not only affects the expression of said promoters or control elements but may affect the metabolism of the transgenic animal itself. It is reiterated that the specification does not disclose a working example of the transgenic animals and the method using said transgenic animals.

In summary, the state of the art of making of transgenic animals is highly unpredictable and unless a transgenic animal has been produced, one can not predict what will the characteristics of a transgenic animal comprising a given expression construct. It is emphasized that USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Therefore, it is concluded that the specification fails to provide any guidance as to how an artisan would have dealt with the art recognized limitations of the method for making any and all transgenic animals and therefore, the creation of any and all non-human transgenic animals and their use in the recited methods would have necessitated undue experimentation on the part of an artisan.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 38, 40, 41, 43, 45, 49, and 65-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Art Unit: 1632

Claim 38 is indefinite because it uses the term "operable". Use of the term "operably" is suggested.

Claim 40 recites the limitation "selected control elements" in line 2. There is insufficient antecedent basis for this limitation in the claim because there is no reference of any selection process of control elements in this claim or in the corresponding independent claim.

Claim 45 is vague and indefinite because it is unclear as to what is meant by the term "a level expression."

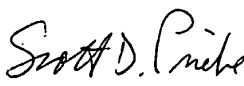
11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Ram R. Shukla, Ph.D.


SCOTT D. PRIEBE, PH.D.
PRIMARY EXAMINER